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Evaluation of antifungal activity of Pistacia atlantica by molecular docking approach

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Dedication:

This thesis is dedicated to my beloved parents, whose unwavering support and encouragement have been my guiding light. To my friends and colleagues, whose camaraderie and insights have enriched my academic journey. And to my mentors, whose wisdom and guidance have been invaluable.

Thank you for believing in me

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Amira

عنوان المذكرة : تقييم النشاط المضاد للفطريات للفستق الاطلسي باستخدام نهج الالتحام الجزيئي

الإسم و اللقب : مداقو سارة - اميرة خياري

المؤطر : لبعل سليم

الملخص :

تسبب الاستخدام المفرط للمبيدات الفطرية بأضرار جسيمة على البيئة وصحة الإنسان. وللحد من هذه المشاكل، يجذب استخدام المبيدات الحيوية الاهتمام العالمي باعتبارها استراتيجية أكثر أماناً مقارنة بالمبيدات الكيميائية التقليدية. ويرجع ذلك إلى قلة مخاطرها على الإنسان والبيئة.

يتمثل عملنا في دراسة النشاط المضاد للفطريات للمركبات الرئيسية للزيت العطري للفستق الأطلسي باستخدام نهج الالتحام الجزيئي باستخدام برنامج MOE لدراسة تفاعل البروتين - الجزيئات لبروتينين مستهدفين 3G5T و7WJO وتسعة عشر مركبًا كيميائيًا من الزيوت الأساسية للفستق الأطلسي.

أظهرت نتائج الإرساء أن أفضل درجات S (بعد درجة S للجزيئات النشطة) كانت لحمض البالمتيك (CID-985) مع 3G5T (-8.0938) ومع البروتين 7WJO (-6.7963). وبالإضافة إلى ذلك، تمت دراسة جوانب مختلفة من الإرتباط بين البروتينين وأفضل جزيء (التفاعلات الكارهة للماء ،التفاعلات الكهروستاتيكية، تفاعلات الأحماض الآمينية)، حيث تميز موقع الارتباط بين البروتينين المستهدفين وأفضل جزيء حمض البالمتيك بشكل عام بالتفاعل الكاره للماء (محب للدهون).

الكلمات المفتاحية : النشاط المضاد للفطريات،المبيدات الفطرية، *in Silico*، *Pistacia atlantica* ، الزيوت الأساسية ، الالتحام الجزيئي ، MOE.

Title of the dissertation: Evaluation of antifungal activity of *Pistacia atlantica* by molecular docking approach

Full name: MEDAKOU sara – KHIARI amira

Directed by: LEBBAL Salim

Abstract:

The excessive use of fungicides has caused severe damage to the environment and human health. To mitigate these problems, the use of biopesticides is attracting global attention as a safer strategy compared to traditional chemical pesticides. This is due to their lower risks to humans and the environment.

Our work involves studying the antifungal activity of the main compounds of the essential oil of *Pistacia atlantica,* using a molecular docking approach with the MOE software to study the protein-ligand interactions between two target proteins, 3G5T and 7WJO and nineteen chemical compounds from essential oils.

The docking results showed that the best S scores (after the S scores of the active molecules) were for Palmitic acid (CID-985) with 3G5T (S score -8.0938) and with the protein 7WJO (S score -6.7963). Additionally, various aspects (hydrophobic interactions, electrostatic interactions, amino acid interactions) were studied in the binding site between the two target proteins and the best molecule, Palmitic acid, indicating in general hydrophobic (lipophilic) interactions.

Key words: antifungal activity, fungicides, *in silico*, *Pistacia atlantica*, essential oils, molecular docking, MOE.

Titre du mémoire: Évaluation de l'activité antifongique de *Pistacia atlantica* par approche de docking moléculaire

Nom et prénom: MEDAKOU sara – KHIARI amira

Encadreur : LEBBAL Salim

Résumé :

L'utilisation excessive de fongicides a causé de graves dommages à l'environnement et à la santé humaine. Pour atténuer ces problèmes, l'utilisation de biopesticides attire l'attention du monde entier, car il s'agit d'une stratégie plus sûre que les pesticides chimiques traditionnels. En effet, les risques qu'ils présentent pour l'homme et l'environnement sont moindres.

Notre travail consiste à étudier l'activité antifongique des principaux composés de l'huile essentielle de *Pistacia atlantica* en utilisant une approche de docking moléculaire avec le logiciel MOE pour étudier les interactions protéine-ligand entre deux protéines cibles, 3G5T et 7WJO et dix-neuf composés chimiques provenant d'huiles essentielles.

Les résultats de l'amarrage ont montré que les meilleurs scores S (après les scores S des molécules actives) étaient ceux de Palmitic acid (CID-985) avec la protéine 3G5T (score S -8,0938) et avec la protéine 7WJO (score S -6,7963). En outre, divers aspects (interactions hydrophobes, interactions électrostatiques, interactions entre acides aminés) ont été étudiés dans le site de liaison entre les deux protéines cibles (3G5T et 7WJO) et la meilleure molécule, Palmitic acid, en indiquant généralement des interactions hydrophobes (lipophiles).

Mots clés : Activité antifongique, fongicides, in silico, *Pistacia atlantica*, huiles essentielles, amarrage moléculaire, MOE.

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List of abbreviations

2D	Two dimensional
3D	Three dimensional
Å	Angstrom (units of length)
Asp	AcideAspartique
Arg	Arginine
ABA	Abscisic Acid
ABTS	Acid 2,2 azino-bis-(3-ethylbenzothiazoline-6-sulfonic)
BMRD	Biological Magnetic Resonance Bank
BHO	Bene Hull Oil
CCG	Chemical Computing Group
DDT	Dichlorodiphényltrichloroéthane
DNA	desoxyribonucleic Acid
EOs	Essential oils
EM	Electron microscopy
EMDB	Electron Microscopy Data Bank
FAO	Food and Agriculture Organization of the United Nations
FACT	Fairness-Accuracy-Confidentiality-Transparency
FAIR	Findable-Accessible-Interoperable-Reusable
FRAP	Ferric Reducing Antioxidant Power Assay
FOs	fixed oils
Glu	Glutamic Acid
Gly	Glycine
HOH	Hydrogen-oxygen-hydrogen
IPM	Integrated pest management
Lys	Lysine
MOE	Molecular Operating Environment
MICs	Minimum inhibitory concentrations
NCBI	National Center Biotechnology Information
NLM	National Library of Medicine
NIH	National Institutes of health

NMR	Nuclear magnetic resonance
PDBe	Protein Data Bank in Europe
PDBj	Protein Data Bank Japan
PLS	Partial Least Squares
PUFAs	polyunsaturated fatty acids
SA	Salicylic acid
SMs	Secondary metabolites
SDF	Structure Data File
SEQ	Sequence
SBDD	Structure-based drug design
Ser	Serine
Thr	Threonine
Try	Tryptophane
U.S	United States
UV	Ultraviolet
Val	Valine
wwPDB	Worldwide Protein Data Bank
X-ray	X-ray diffraction

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Introduction

In recent years, there has been an increase in the number of diseases caused by bacterial, fungal, and viral infections. Infections affect plants at different stages of agricultural production. Depending on weather conditions and the phytosanitary condition of crops, the prevalence of diseases can reach 70–80% of the total plant population, and the yield can decrease in some cases down to 80–98% **(Nazarov et al, 2020).** Fungal diseases are an ongoing threat to the global agricultural industry, and their pathogens are a major threat to global agriculture and result in significant economic losses annually. The Food and Agriculture Organization of the United Nations (FAO) estimates that plant diseases, including fungi, cost the global economy about US$ 220 billion annually, with 20-40% of crop production lost. Crop-pathogenic fungi are responsible for the loss of up to 20% of global crop yields, which are a food source for about 600 million people annually. Fungal diseases severely damage major agricultural crops, with at least 125 million tons of agricultural production destroyed each year. In addition to direct damage to crops, many fungal diseases produce harmful toxins, posing a significant threat to human and animal health **(Nizamani et al, 2024).**

To control the scourge of plant diseases, farmers have used pesticides to manage the damage of plant. Chemical controls (pesticides) are often the dominant tactic used in IPM programs. Chemical controls are designed to reduce pest (insect, pathogen, rodent, etc.) populations below levels that will not negatively impact the crop **(Brunner, 1994).** This method is encouraged as the last resort to complement other methods or to address major pest outbreak problem **(Adeniyi & Asogwa, 2023).** Pesticides are used to suppress, eradicate or prevent organisms which are considered harmful to crops or nuisance **(McGinley et al, 2023).**

Insecticides, herbicides, and fungicides, the three major types of pesticides classified by their target organisms, are currently being used in agriculture worldwide at around 2.7 million tonnes per year **(Ding et al, 2023).** Pesticides are classified into two major categories based on their physical and chemical properties. Pesticide classification by nature of pesticide (synthetic and natural) and acting on pest type **(Pathak et al, 2022).**

The global pesticide consumption in 2019 was approximately 4.19 million metric tons, where China was by far the largest pesticide-consuming country (1.76 million metric tons), followed by the United States (408 thousand tons), Brazil (377 thousand tons), and Argentina (204 thousand tons) **(Rajak et al, 2023),** and France saw an increase in pesticide

use, making it one of the largest consumers of pesticides in Europe and the world **(Martin et al, 2023).** Furthermore, India belongs to one of the major pesticide producing countries in Asia, having 90 thousand tons annual production of organochlorine pesticides including benzene hexachloride and DDT **(Pozo et al, 2011).** Total pesticides trade reached approximately 7.2 Mt of formulated products in 2020, with a value of USD 41.1 billion **(FAO, 2022).**

The use of pesticides for pest and disease control has increased agricultural production worldwide, but has also led to increased negative impacts on land use, the environment, and human exposure to various pesticide residues. Another important external effect is the unintended destruction of beneficial predators of pests **(Coria & Elgueta, 2022)**. Those materials have been thought as probable mutagens as they comprise constituents to trigger deviations in DNA. According to the world health organization (WHO), about 1000,000 human being are affected by acute poisoning by contact with pesticide **(Hassaan & El Nemr, 2020).** Besides, nearly 90% of pesticide use in the USA is in the agricultural sector, making agricultural laborers or farm workers and their families particularly vulnerable to the effects of these dangerous chemicals **(Donley et al, 2022).**

To prevent the problems resulted from chemical control, many alternative methods were proposed such as:

- **Biological control:**

Biological control, or biocontrol, is the exploitation of living agents to combat pestilential organisms (incl. pathogens, pests, and weeds) for diverse purposes to provide human benefits **(Stenberg et al, 2021),** is playing an established role in vector control. The biological control method is innovative and sustainable way to control pests. This method leaves no chemical residues and has no harmful impact on the humans or other organisms. If the method is successfully implemented following introduction, it may provide a permanent control with favorable cost–benefit ratio **(Kumari et al, 2022).** Biological control suppresses pests via the action of their living natural enemies **(Stoner, 1995).** Categories of natural enemies, in order of frequency of use in biological control, include: parasitoids (parasitic wasps and flies that require only a single host in which to complete their development); predators (insects, spiders and predatory mites that must consume many prey individuals to complete their development); pathogens (bacteria, fungi and viruses); parasites (soil-inhabiting entomopathogenic nematodes); and antagonists (less damaging competitors) **(Mills & Daane, 2005).**

- **Cultural control:**

Cultural controls are manipulations of the agroecosystem that make the cropping system less friendly to the establishment and proliferation of pest populations. Maintaining and increasing biological diversity of the farm system is a major strategy of cultural control. Genetic diversity of crops and species diversity of the associated plant and animal community could be effective approaches in cultural practices **(Zaefarian & Rezvani, 2016).** Biological controls and cultural controls provide valuable alternatives to organophosphate pesticides (OPs) for the suppression of major arthropod crop pests **(Mills & Daane, 2005).**

- **Physical control:**

Physical control refers to mechanical or hand controls where the pest is actually attacked and destroyed. Physical controls are used mostly in weed control. Tillage, fire, removal by hand, grazing and mowing are all used to destroy weeds and prevent reproduction. Some insects may also be destroyed by tillage, which destroys their eggs or overwinter stages of growth. Weeds are not controlled through a single operation **(Singh & Pandey, 2012).** Physical control methods include all techniques whose primary mode of action does not involve biological or biochemical processes, these techniques can be broadly divided into four main categories: thermal control, electromagnetic control, mechanical control and pneumatic control **(Aubertot e al, 2005).**

- **Genetic controls:**

These strategies rely on the use of genetically modified strains of pests to achieve two main goals. The first is to reduce the density of natural populations of the target pests or eliminate the mal together. The second goal is to replace natural pests with less harmful individuals. These strategies are also known as gene drives, which rely on the super Mendelian inheritance of selfish patterns of inheritance. These patterns help transfer important genetic material, such as disease resistance or lethality genes, into natural populations. These components are commonly referred to as gene drives **(Legros et al, 2021).**

- **Use of biopesticides:**

Biopesticides are the biological agents used to control the pest population. It includes the use of botanicals, microbial pathogens such as fungi, bacteria, viruses and natural enemies of pests such as parasitoids and predators, nematodes and semiochemicals. Biopesticides play an important role in sustainability of agricultural bioeconomy. The

ecosystem benefits rendered by the agriculturally important biological resources warrant inclusion of biopesticides in Integrated Pest Management Programmes **(Rajamani & Negi, 2021).** Natural products and micro-organisms have been used as biopesticides worldwide as they can be sourced from the environment, they are generally safe to non-target organisms including humans, they have reduced persistence in the environment, and they are potentially acceptable for use in organic agriculture. Compared with synthetic pesticides, new biopesticides can gain regulatory approval faster. They can also be developed in less time and are much less expensive to develop **(Liu et al, 2021).** Moreover, biopesticide is gaining interest because of its advantages associated with the environmental safety, target-specificity, efficacy, biodegradability and suitability in the integrated pest management (IPM) programs. Thus, biopesticide is one of the promising alternatives to manage environmental pollutions. Although use of agrochemicals is indispensable to meet the ever growing demands of food, feed and fodder, opportunities do exist in selected crops and niche areas where biopesticides can be used as a component of IPM. Through wider application of biopesticides in agriculture and health programs, environmental safety can be beneficially affected **(Kumar & Singh, 2015).**

On the other hand, Algeria has a rich and varied flora because of its geographical location and extensive and varied vegetation cover. Among the flora, *Pistacia atlantica* commonly referred to as "Betoum", is one of the many plants that grow spontaneously in Algeria and belongs to the Anacardiaceae family **(Benmohamed et al, 2023).** *P. atlantica* has many medicinal properties such as antioxidant, antidiabetic, antihyperlipidemic, along with others. It can also be effective in gastrointestinal diseases. Thus, different new drugs can be formulated based on *P. atlantica* for the management of various diseases **(Mahjoub et al, 2018).**

In addition, bioinformatics and the management of scientific data are critical to support life science discovery. As computational models of proteins, cells, and organisms become increasingly realistic, much biology research will migrate from the wet-lab to the computer **(Lacroix & Critchlow, 2003).** Currently, computer simulations, or *in silico* experiments, are being increasingly employed to predict the behavior of plants under different environmental conditions **(Baranoski et al, 2012).** These *in silico* methods currently play a guiding role in the evaluation of products for which no data are available **(Claude & Guillouzo, 2009).** Furthermore, *in silico* testing makes it possible to generate thousands of different simulation scenarios and virtual patients. What's more, companies

see a reduction in the time and costs involved in conducting clinical studies, while benefiting from an accelerated pathway for new products **(Renard, 2022).**

In this context, the aim of the present study is the evaluation of antifungal effect of extract from *Pistacia atlantica* using a molecular docking approach. The manuscript will be divided into two parts: A first one devoted to material and methods; while the second part presenting the results obtained and their discussion.

Chapter one:
Materials & Methods

The main aim of our Master's thesis is to test the antifungal effect of certain compounds in *Pistacia atlantica* essential oils by using a molecular docking approach.To do this, we used the following material:

I. Materials:

1.1. Microcomputer:

In our study we used a microcomputer with 4GB memory, Intel(R) Celeron(R) CPU N3060 @ 1.60GHz 1.60GHz, processor 64-bit operating system, ×64-based processor. The software used is installed under Windows 10 PRO operating system.

1.2. Data Banks:

1.2.1. PubChem database (Figure 1)

PubChem (https://pubchem.ncbi.nlm.nih.gov) **(Bolton et al, 2008)** is a public chemical database at the National Center for Biotechnology Information (NCBI) **(Sayers et al, 2021)** of the National Library of Medicine (NLM), an institute within the U.S. National Institutes of Health (NIH). It collects chemical information from more than 750 data sources and disseminates it to the public free of charge **(Kim et al, 2020).** It is one of the top five most visited chemistry websites in the world, with more than five million unique users per month (as of March 2020) **(Kim et al, 2021),** with more than four million unique interactive users per month at peak time. With millions of users every month, PubChem is a popular resource that serves a wide range of audiences, including researchers, chemical health and safety officers, patent agents, educators, and students **(Kim et al, 2023).** It started in 2004 serving as a public repository for information generated from chemogenomic, medicinal chemistry and functional genomics research **(Wang et el, 2017).** Importantly, used in many artificial intelligence and machine learning studies, PubChem is widely used as a 'big data' source in machine learning and data science studies for virtual screening **(Singh et al, 2020),** drug repurposing **(Huang et al, 2015),** chemical toxicity prediction **(Lee et al, 2017)** and metabolite identification **(Ludwig & Böcker, 2018)** and so on. This database consists of three linked databases: Substance (containing depositions of chemical samples), BioAssay (containing biological

results for small molecules and RNAi reagents) and Compound (containing unique chemical structures derived from Substance) **(Cheng et al, 2014).**

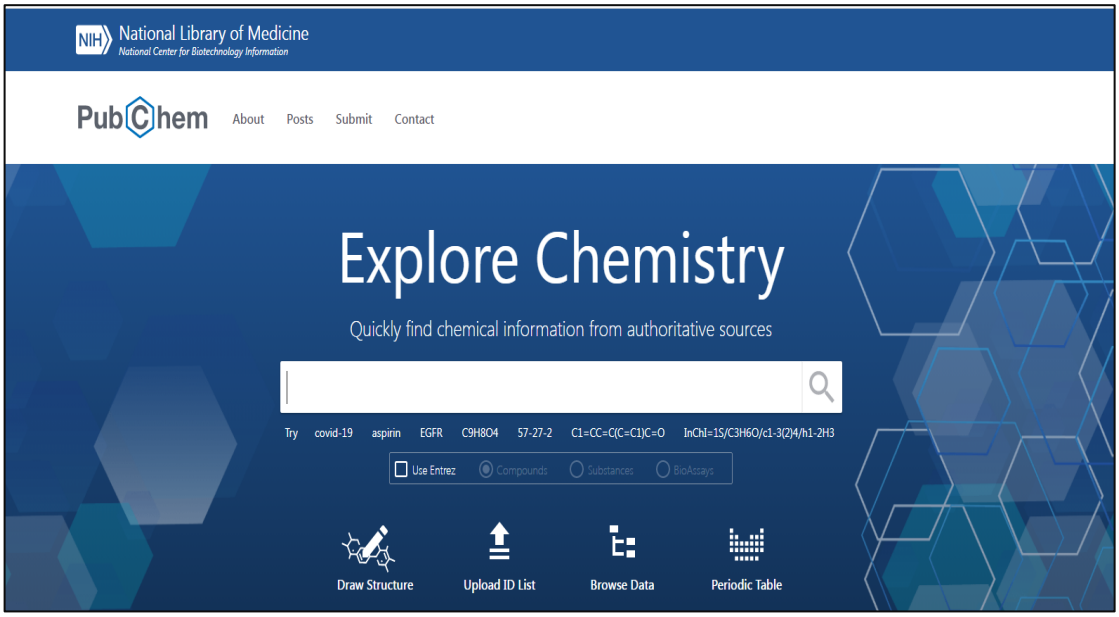


Figure 1: Homepage of PubChemdatabase

1.2.2. PDB (Protein Data Bank) (Figure 2)

The Protein Data Bank is the single global repository for experimentally determined structures of biological macromolecules and their complexes **(Burley et al, 2017)**. Nowadays, it is a vital tool for anyone involved in protein studies from biological, biochemical or therapeutic points of view, in addition to educational purposes, as recently highlighted by the COVID-19 pandemic. Following the first (X-ray) protein structures discovered in the 1950s and 1960s, the need for an open repository for crystallographic data rapidly arose **(Santos & Pessoa, 2023).**

It was established in 1971 at Brookhaven National Laboratory with seven structures **(Bernstein et al, 1977)**, the PDB contains (As of March 2023) over 200,000 structures of biological macromolecules **(Choudhary et al, 2023)**, to become the only freely accessible global archive of 3D structures of proteins, nucleic acids, and their complexes with one another and small-molecule ligands experimentally **(Burley et al, 2022).** The PDB is the first open-access digital resource in biological sciences and is managed by the worldwide Protein Data Bank (wwPDB) organization **(Young et al, 2018)**. The Protein Data Bank archives atomic coordinates of macromolecular structures determined using" X-ray, NMR

and EM". The PDB also archives multi-method structures that are based on one of the traditional methods (X-ray, NMR or 3DEM) used in combination with methods such as neutron diffraction or SAS **(Vallat et al, 2021).** The PDB is utilized by many millions of basic and applied researchers, educators, and students working across fundamental biology, biomedicine, bioengineering, biotechnology and energy sciences **(Burley et al, 2023).**

The Worldwide Protein Data Bank (wwPDB, wwpdb.org) **(Berman et al, 2003)** manages the PDB archive according to the FACT principles of Fairness-Accuracy-Confidentiality-Transparency **(van der Aalst et al., 2017)** and the FAIR principles of Findable-Accessible-Interoperable-Reusable **(Wilkinson et al., 2016)**. Current wwPDB members include RCSB Protein Data Bank (RCSB PDB), **(Burley et al., 2019)**, Protein Data Bank in Europe (PDBe) **(Mir et al., 2018)**, Protein Data Bank Japan (PDBj) **(Kinjo et al., 2018)**, the 3DEM data resource Electron Microscopy Data Bank (EMDB) **(Abbott et al., 2018)**, and the NMR data resource of Biological Magnetic Resonance Bank (BMRB) **(Ulrich et al, 2007).**

Its website is: https://www.rcsb.org/.

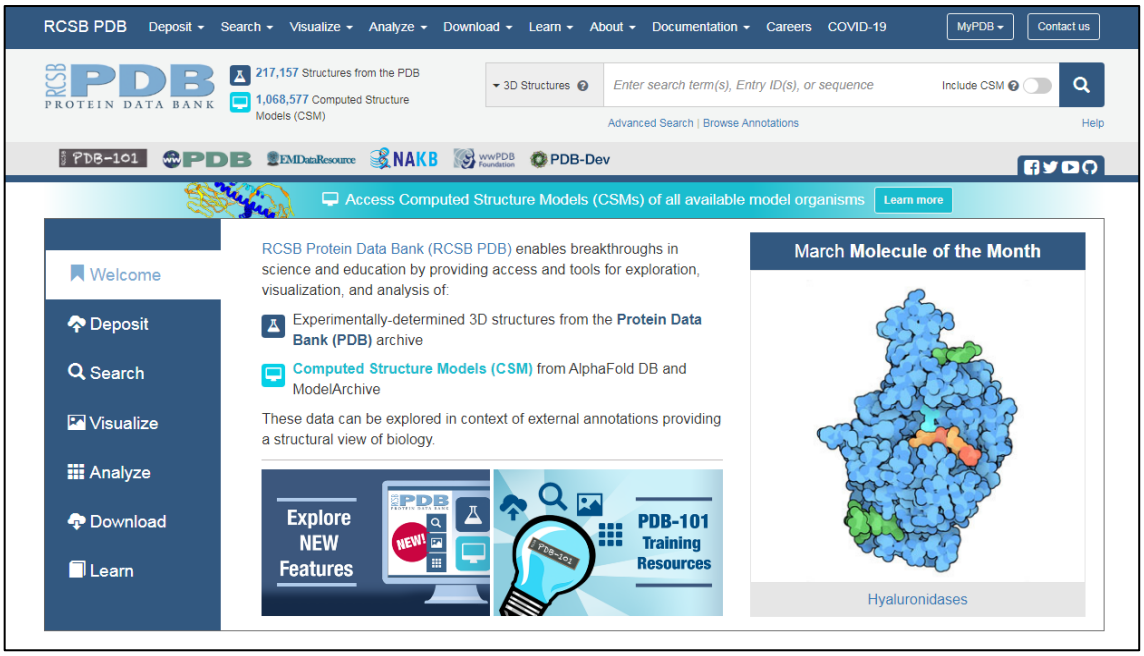


Figure 2: PDB (Protein Data Bank) homepage

1.3. Programs:

1.3. MOE (Molecular Operating Environment) (Figure 3)

Molecular docking analysis was carried out to predict the binding sites between two proteins and nineteen compounds using the MOE 2014.0901. The MOE (Molecular Operating Environment) is a comprehensive software system for pharmaceutical and life sciences developed by Chemical Computing Group ULC (CCG) (Canada) **(Özdemir et al, 2022).** It is a comprehensive application environment and technology development platform that integrates visualization, simulation, and application development. MOE supports drug design in a unified operating environment through molecular modeling, protein structure analysis, small molecule data processing, and protein and small molecule docking research **(Fu et al, 2020).**

Molecular Operating Environment are employed by biologists, medicinal chemists and computational chemists in the field of pharmaceutical, biotechnology and academic research **(Liu e al, 2022).**

Figure 3: Graphical surface of the MOE package

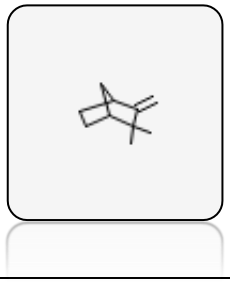
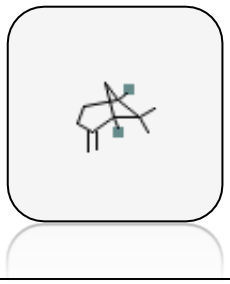
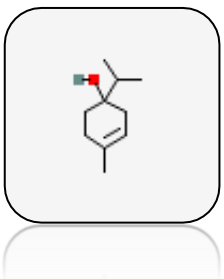
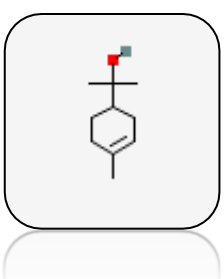
II. Methods

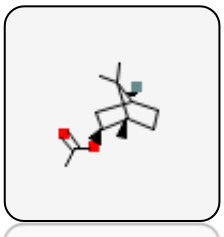
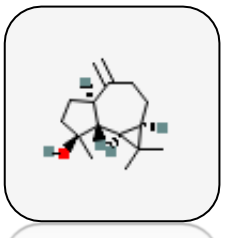
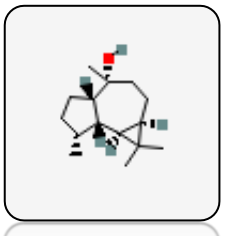
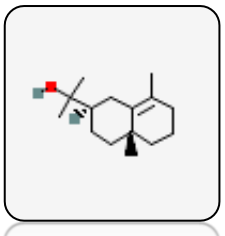
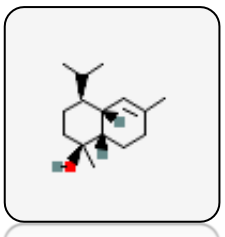
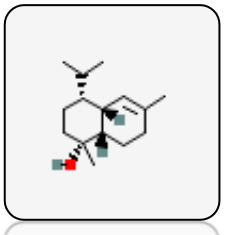
2.1. Database

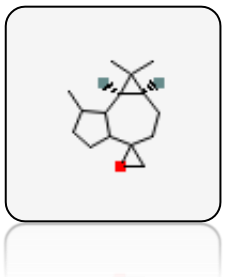
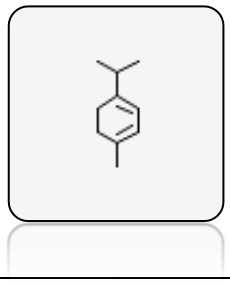
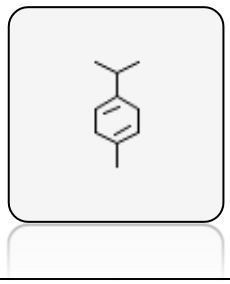
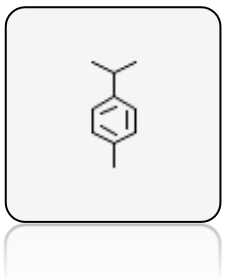
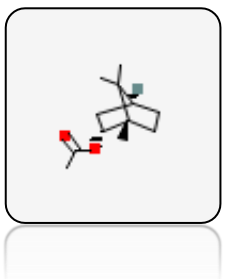
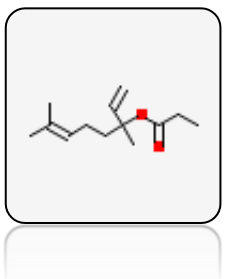
2.1.1. Choice of compounds

Chemical composition of essential oils of *Pistacia atlantica* was taken from three published articles and they are listed in the appendix. We have chosen 19 compounds as ligands for molecular docking (Table 2) due to their high rates. In addition, two active molecules specific to each target (Table 03) and included in the composition of the pesticides were also studied.

Table 1: List of studied molecules (ligands) **(PubChem database)**

PubChem code	Compound	Structure 2D	Molecular formula
CID 6616	Camphene		C10H16
CID 14896	β-Pinene		C10H16
CID 11230	Terpinen-4-ol		C10H18O
CID 17100	α-Terpineol		C10H18O

CID 6950273	Isobornyl acetate		C12H20O2
CID 92231	Spathulenol		C15H24O
CID 92812	Ledol		C15H26O
CID 6432005	γ-Eudesmol		C15H26O
CID 3084331	epi-α-Muurolol		C15H26O
CID 91753440	α-Muurolol		C15H26O

CID 91746712	allo-Aromadendrene epoxide		C15H24O
CID 7462	α -Terpinene		C10H16
CID 7461	ɣ-Terpinene		C10H18O
CID 7463	p-Cymene		C10H14
CID 93009	Bornyl acetate		C12H20O2
CID 61098	Linalyl propionate		C13H22O2

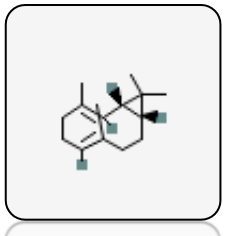
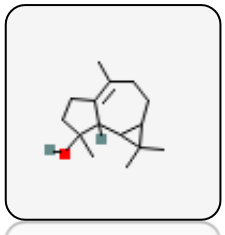
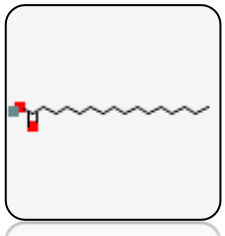
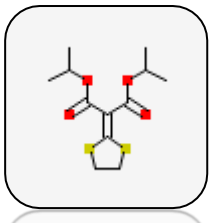
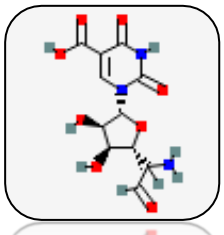
CID 13894537	Bicyclogermacrene		C15H24
CID 14038848	Isospathulenol		C15H24O
CID 985	Palmitic acid		C16H32O2

Table 2: Active molecule with their target enzyme **(PubChem database)**

Active molecules	**code**	**Structure 2D**	**Molecular formula**	**Targets enzymes**
Isoprothiolane	39681		C12H18O4S2	3G5T
Polyoxin	3084093		C11H13N3O8	7WJO

2.1.2. Preparation of the database:

Compounds were prepared for molecular docking using MOE in accordance with the following steps:

- Open the Pubchem website: https://pubchem.ncbi.nlm.nih.gov/
- Compounds were downloaded in SDF format;
- We open the MOE software
- Then we click: file; then: new; Then go to: Database
- In the database window, click on : File ; Then : import
- And : Add the different studied compounds;
- Hydrogen molecules were displayed and adjusted as required by using the display tool On tab compute; we click on (molecule) then (partial charges) then we select 'Hydrogens and lone pairs as required';
- Using the compute tool, then Energy Minimize, the OH groups were optimally oriented
- Finally, the prepared database must be backed up.

2.2. Target proteins

2.2.1. Choice of proteins:

We choose two proteins: 3G5T and 7WJO (Table 03). These proteins were downloaded from protein data bank (PDB), the choice of different proteins that we have studied according to:

- The best resolution (preferably lower by 2 Å);
- The presence of a ligand;
- The chosen proteins are known targets for chemical fungicides.

Table 3: The crystallographic data for the protein 3G5T **(PDB)**

Protein	PDB code	Classification	Resolution	Ligands
Crystal structure of trans-aconitate 3-methyltransferase from yeast	3G5T	Transferase	1.12 Å	SAH

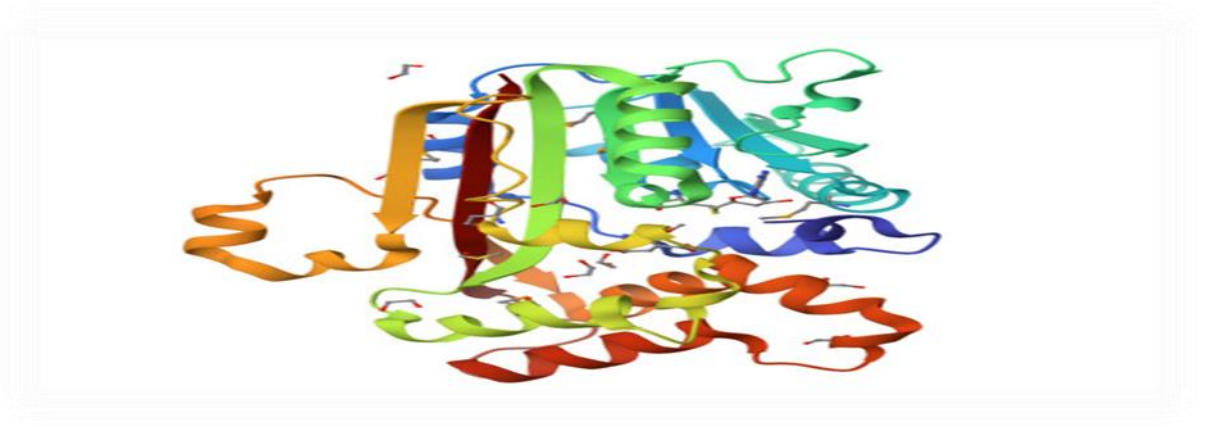


Figure 4: 3D structure of the 3G5T protein

Table 4: The crystallographic data for the protein 7WJO **(PDB)**

Protein	PDB code	Classification	Resolution	Ligands
CryoEM structure of chitinsynthase 1 from *Phytophthora sojae* complexed with nikkomycin Z	7WJO	Transférase	3.20 Å	BGI

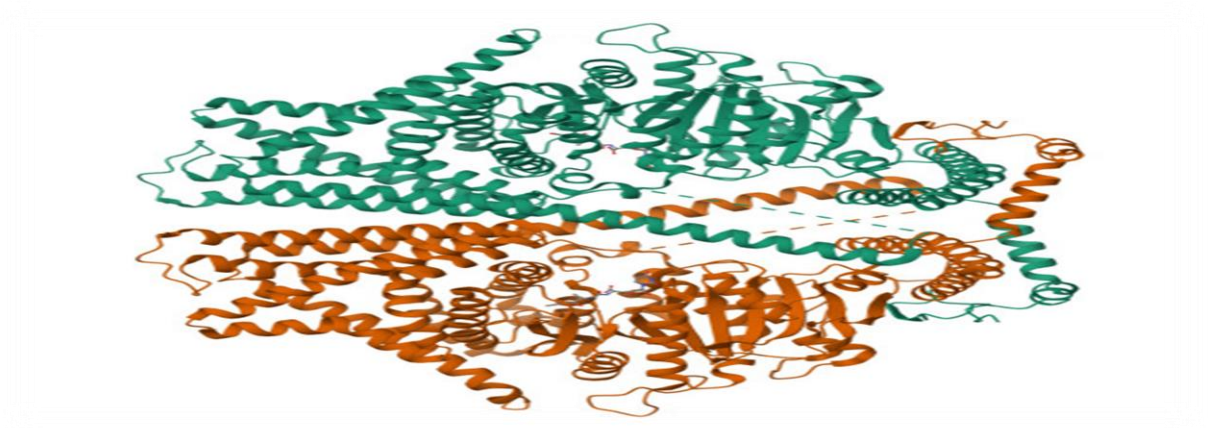


Figure 5: 3D structure of the 7WJO protein

2.2.2. Download and Preparation

- We Open the PDB website then we search for (3G5T or 7WJO) and we download files choosing PDB format;
- After that, we open the MOE program;
- We click on Open and choose the protein to be studied;
- We click on SEQ and remove the HOH chain and additional links;
- Click on LigX ;
- The prepared proteins were saved

3. Molecular Docking

Molecular Docking has become an essential aspect of in-silico drug development in recent years **(Agu et al, 2023).** Since first being developed in the 1980s **(Stanzione & Cole, 2021),** Molecular Docking is a modeling tool of Bioinformatics, and has come out to be a novel concept with various types of advantages. It behaves as a highly exploring domain due to its significant structure-based drug design (SBDD**) (Sharma et al, 2021).**

The main aim of this technique is to predict the placement of small molecules or ligands within the active site of their target protein (receptor). It is mainly used to accurate estimation of most favorable binding modes and bio-affinities of ligands with their receptor, presently it has been broadly applied to virtual screening for the optimization of the lead compounds **(Surabhi & Singh, 2018).**

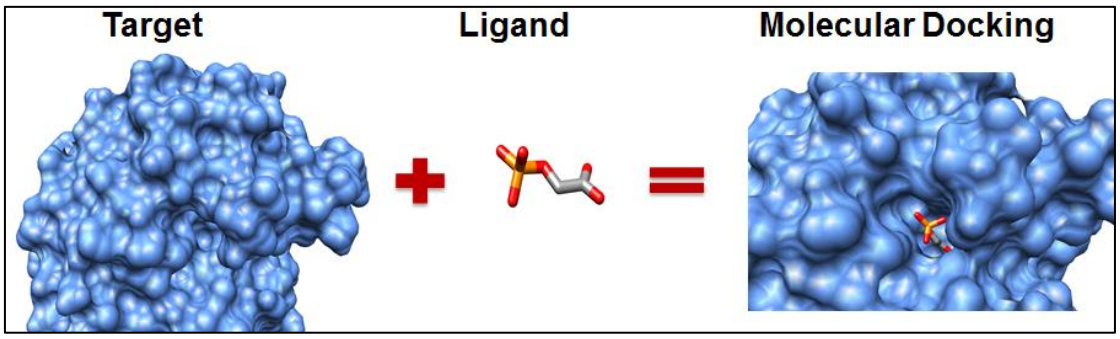


Figure 6: Process of Docking **(Hernández-Santoyo et al, 2013).**

Over the last two decades, more than 60 different docking tools and programs have been developed for both academic and commercial, use such as DOCK **(Venkatachalam et al, 2003)** AutoDock **(Österberg et al. 2002),** FlexX **(Rarey et al. 1996),** GOLD **(Jones et al, 1997),** ICM **(Schapira et al, 2003),** MOE-Dock **(Corbeil & Labute, 2012)** and many others **(Pagadala & Tuszynski, 2017).**

In our investigation, the study of the interaction between the active site of the two proteins (3G5T and 7WJO) and 19 ligands to form a stable complex is carried out using MOE software, according to the following steps:

Open MOE software

- First, click on : Open ;
- then we choose the ready-made enzyme (3G5T or 7WJO), and click on : compute ; Then dock;
- We define rigid receptors of the docking protocol (in the open window);
- For ligand you must select an MDB File (Prepared database);
- Next : we hold 10 poses then we play *Run*

After docking results have been displayed;

- We click on the best S score (double-click);
- Then we change the colors of the protein and the best ligand;
- Next click on: Atom.....Residues ;
- After that, we save the picture

To show neighboring amino acids, we proceed as following steps:

- We click on ligand (right) then on ligand interactions;
- Next, click on: Export and save the image (in the desired format and resolution).

To study the various thermodynamic parameters, we follow the next steps:

- Click on: surface, then select: surface & Maps.
- In the Color option, we select: Lipophilia; and click on Create.
- We repeat the same steps.

For lipophilicity (hydrophobic) and pocket electrostatics, we make the following changes after making the following changes:

- Atoms: ligand atoms (instead of receptor atoms).
- Near: pocket atoms (instead of ligand atoms).
- Save photos.

Chapter Two:
Results & Discussion

1. Results

1.1 S score results

We remark in the tables 05 & 06 that the ligand ***Palmitic acid*** (CID-985) had the best results of the binding interaction with the protein 3G5T (- 8.0938); following *Linalyl propionate* (- 6.1474). Similarly, it gave the best S score with the protein 7WJO (- 6.7963).

Table 05: S score of the tested ligands with two target proteins.

Molecule (ligand)	Pubchem code	3G5T dock results	7WJO dock results
Camphene	6616	-3.7247	- 4.4691
β-Pinene	14896	- 4.1503	- 4.3017
Terpinen-4-ol	11230	- 4.2341	- 4.7227
α-Terpineol	17100	- 4.9188	- 4.9115
Isobornyl acetate	6950273	- 3.8929	- 5.1689
Spathulenol	92231	- 4.2616	- 5.3265
Ledol	92812	- 3.5879	- 4.8516
γ-Eudesmol	6432005	- 4.1372	- 5.9123
epi-α-Muurolol	3084331	- 3.9300	- 5.2521
α-Muurolol	91753440	- 3.8881	- 5.1527
allo-Aromadendrene epoxide	91746712	- 3.8086	- 5.1075
α -Terpinene	7462	- 4.7831	- 4.3972
Ɣ-Terpinene	7461	- 4.5000	- 4.3690
p-Cymene	7463	- 4.8955	- 4.4320
Bornyl acetate	93009	- 4.7787	- 5.0989
Linalyl propionate	61098	- 6.1474	- 5.7272
Bicyclogermacrene	13894537	- 3.7531	- 5.0461
Isospathulenol	14038848	- 4.2614	- 5.3402
Palmitic acid	985	- 8.0938	- 6.7963

Table 06 : S score of the active molecule

Active Molecule	Pubchem code	S score
Isoprothiolane	39681	- 6.0113
Polyoxin	3084093	- 6.0342

We remark that for both 3G5T and 7WJO, the best ligand was the same (Palmitic acid).

The green part in Figures 7 and 8 represents the best ligand, while the purple part is the active site of the target enzyme.

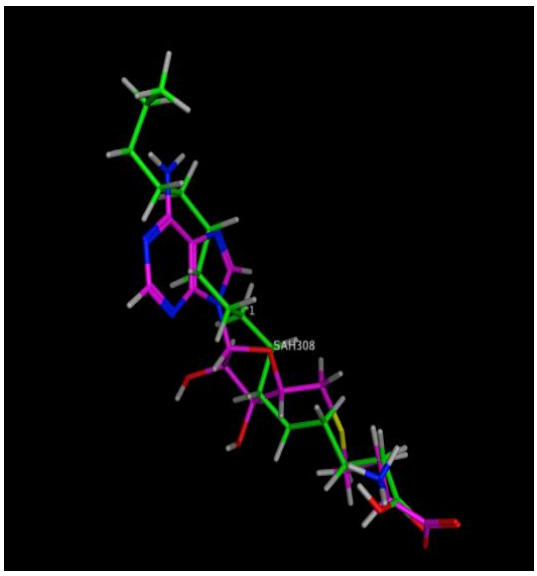


Figure 7: Active site of 3G5T and interaction with *Palmitic acid*.

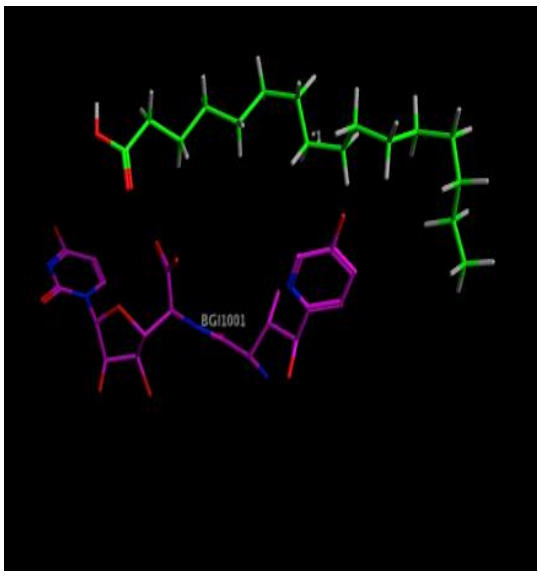


Figure 8: Active site of 7WJO and interaction with *Palmitic acid*.

1.2. Characteristics of association between the target proteins and the best ligands

A. Interactions with amino acids :

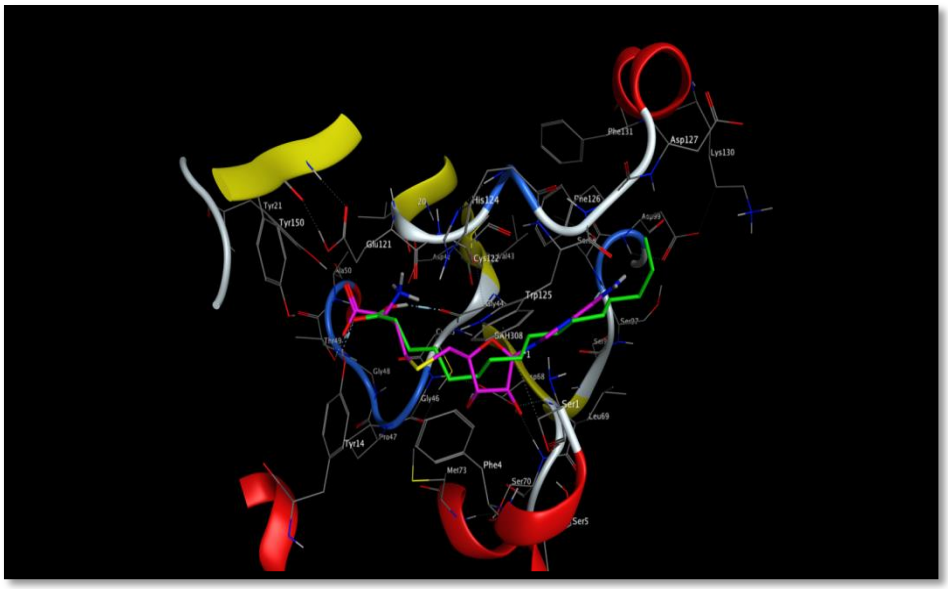


Figure 9: Residues near *Palmitic acid* binding site with 3G5T

For 3G5T protein, the Figure 10 shows close links between palmitic acid and seven amino acids: Val120, Gly44, Tyr21, Thr49, Tyr14, Asp68 and Ser98.

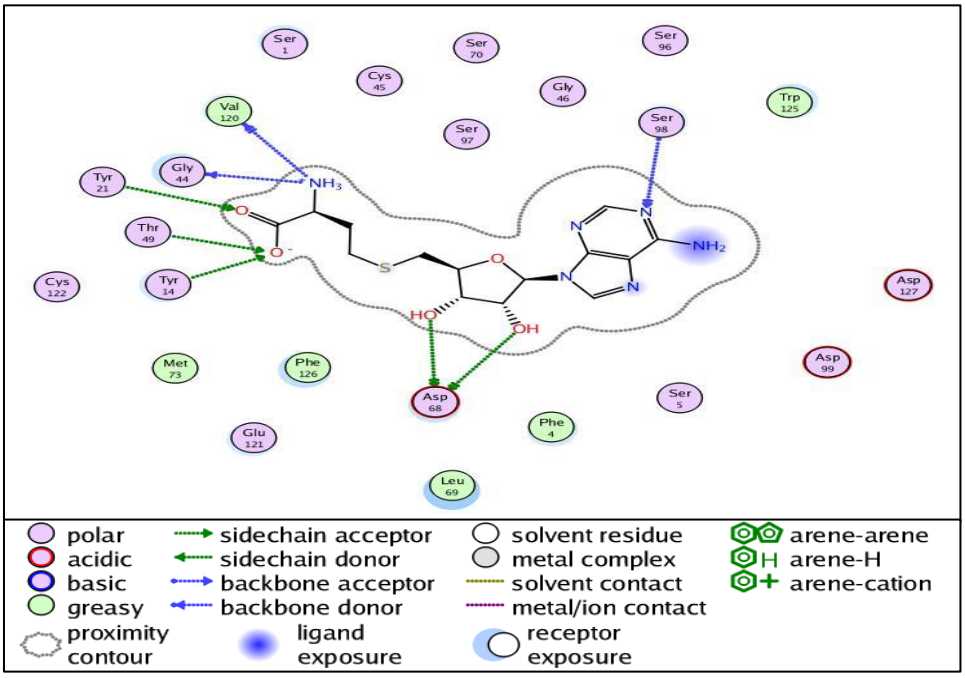


Figure 10 : Amino acids present in the binding site for the association 3G5T - *Palmitic acid*

Figure 11: Residues near *Palmitic acid* binding site with 7WJO

For 7WJO protein, the Figure 12 shows close links between palmitic acid and six amino acids: Arg538, Lys358, Asp291, Asp382, Glu241 and Thr237.

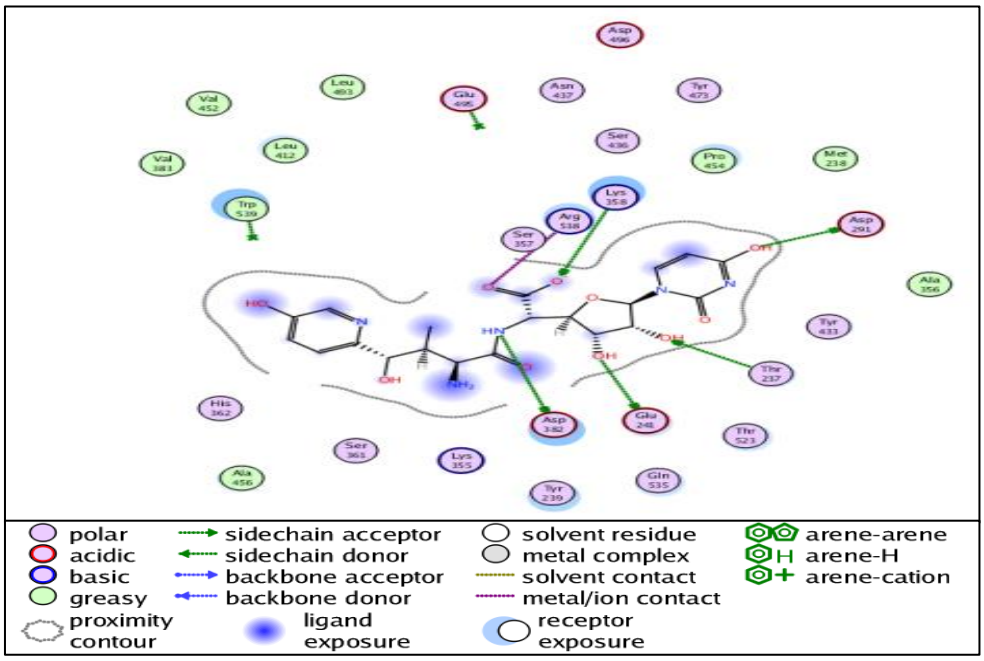


Figure 12: Amino acids present in the binding site for the association 7WJO - *Palmitic acid* ligand

B. Electrostatic interactions:

Interactions between 3G5T and CID-985 Palmitic acid ligand

Figure 13 shows the blue color appears strongly in the interaction site between 3G5T and the best *Palmitic acid* ligand comparatively to the red and white, which mean the dominance of positive charges.

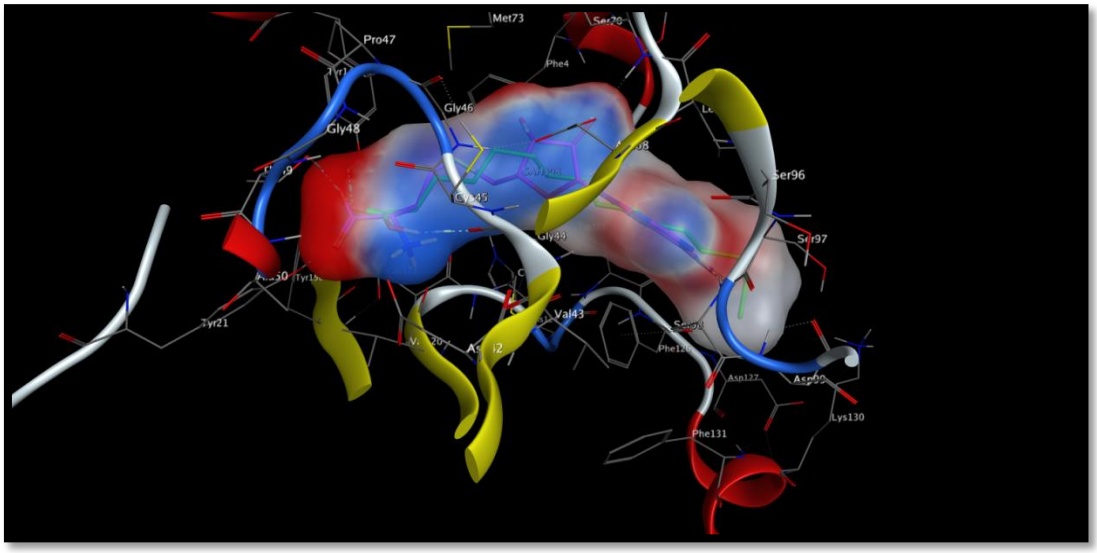


Figure 13: 3G5T - CID 985 electrostatic pocket interactions

Figure 14 shows that the electrostatic interaction between 3G5T and the best Palmitic acid ligand is characterized by a mixture of charges; red surfaces (atoms with negative charges) and white surfaces (atoms with neutral charges) were observed.

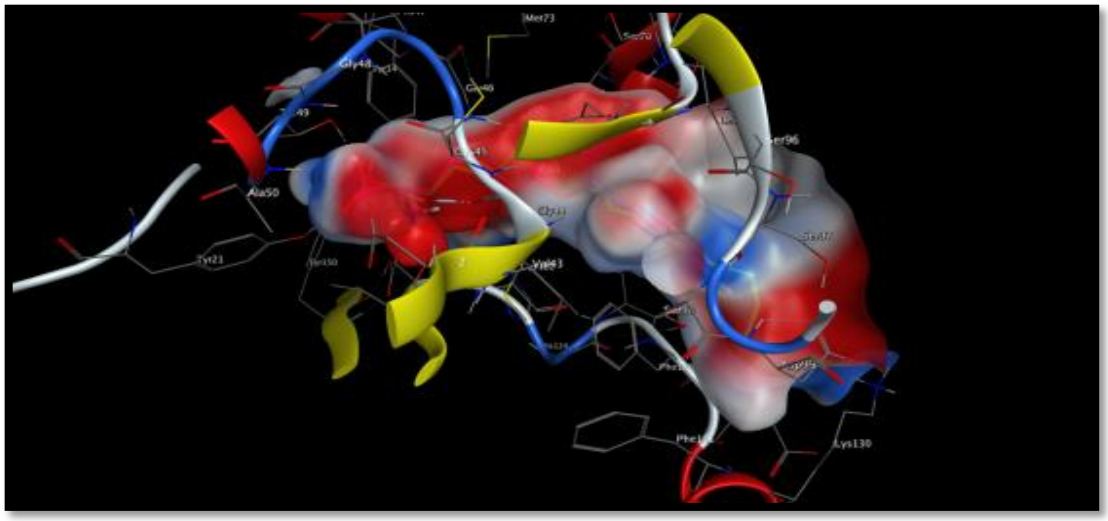


Figure 14: 3G5T - CID 985 electrostatics interactions

Interactions between 7WJO and CID-985 Palmitic acid ligand

Figure 15 shows the dominance of neutral charges in the interaction site between 7WJO and the best *Palmitic acid* ligand.

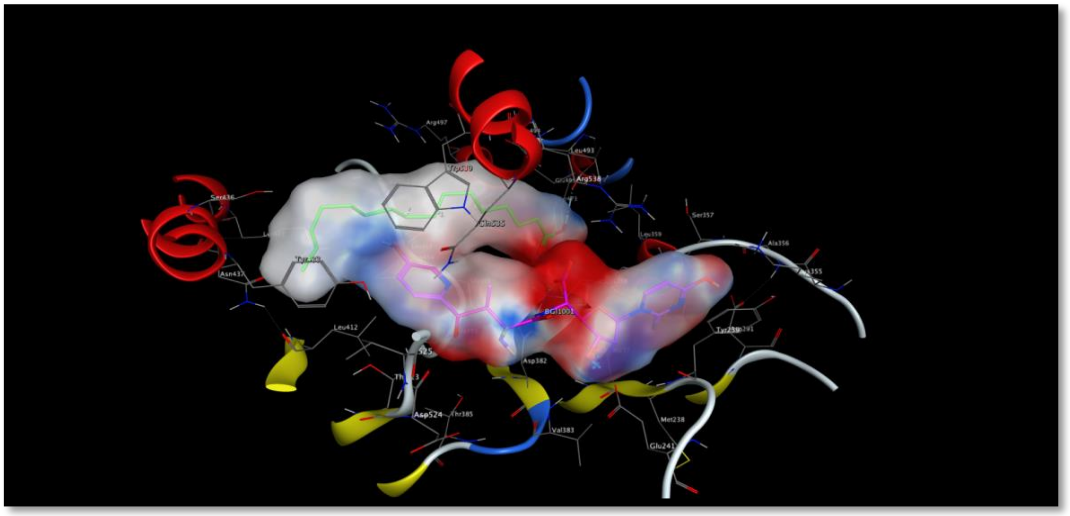


Figure 15: 7WJO - CID 985 electrostatic pocket interactions

Figure 16 shows that the electrostatic interaction between 7WJO and the best Palmitic acid ligand is characterized by a mixture of charges; surfaces were observed in white, (atoms with neutral charges).bleu (atoms with positive charges), and red, (atoms with negative charges).

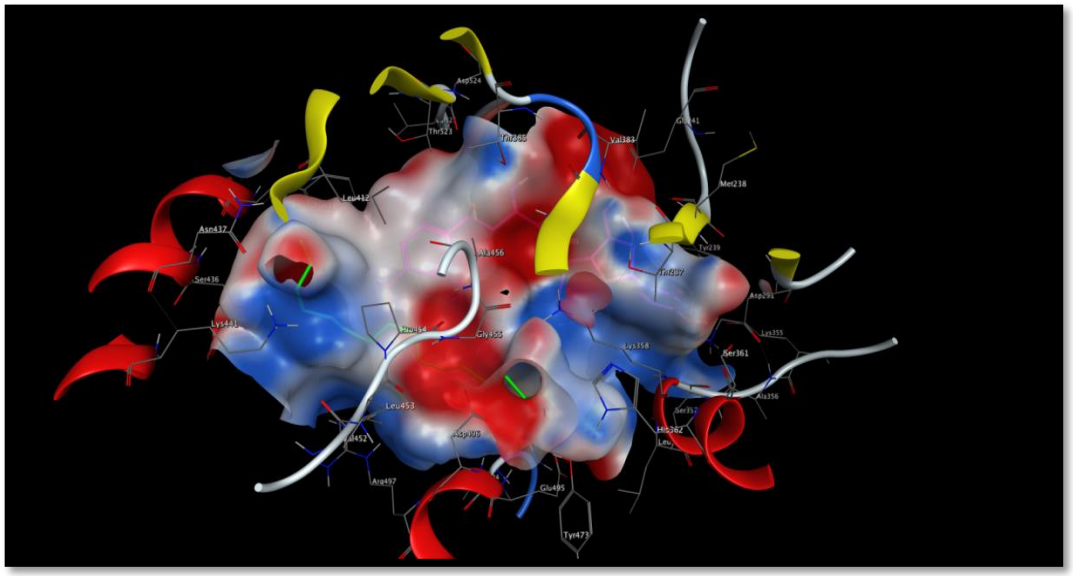


Figure 16: 7WJO - CID 985 electrostatics interactions

C. Hydrophobic interactions (Lipophilicity):

Lipophilicitic interactions between 3G5T and CID-985 Palmitic acid ligand

Figure 17 Shows that the binding site of 7WJO with the best T-Muurolol ligand is lipophilic we observed most of the receptor regions are green in colour (lipophilic atoms).

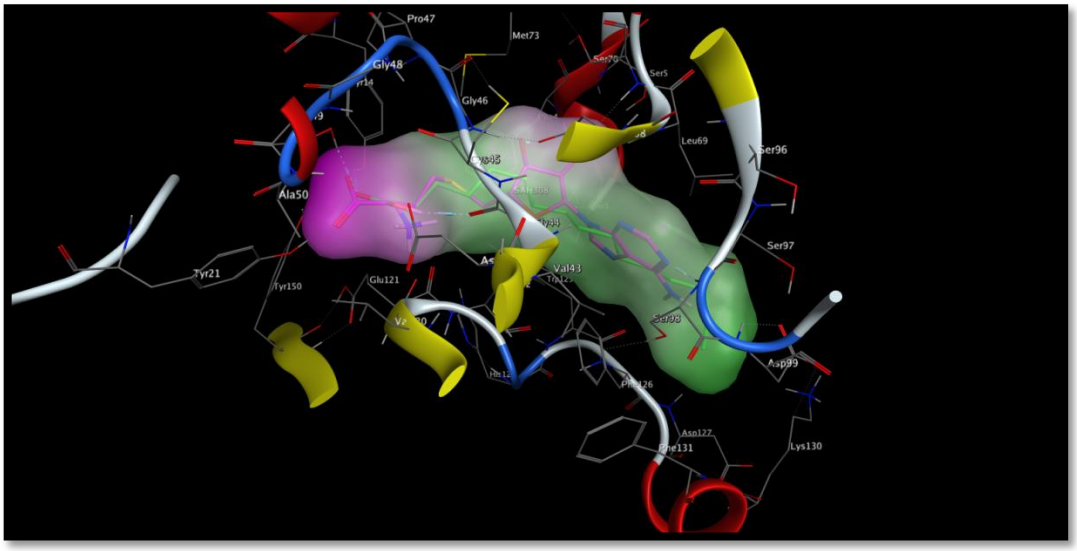


Figure 17: 3G5T - CID 985 pocket lipophilicity

Figure 18 shows that the purple color appears strongly, indicating the existence of a hydrophilic interaction (lipophob).

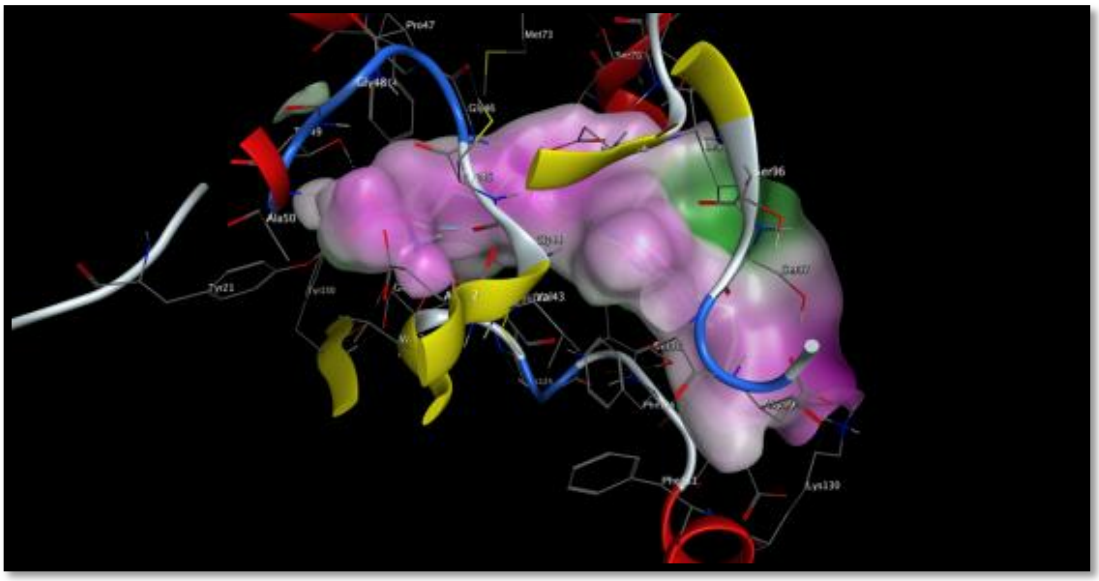


Figure 18: 3G5T - CID 985 lipophilicity

Lipophilicitic interactions between 7WJO and CID-985 Palmitic acid ligand

We notice that there is dominance of the green color, which means existence of hydrophobic interaction (lipophile) (Figure 19).

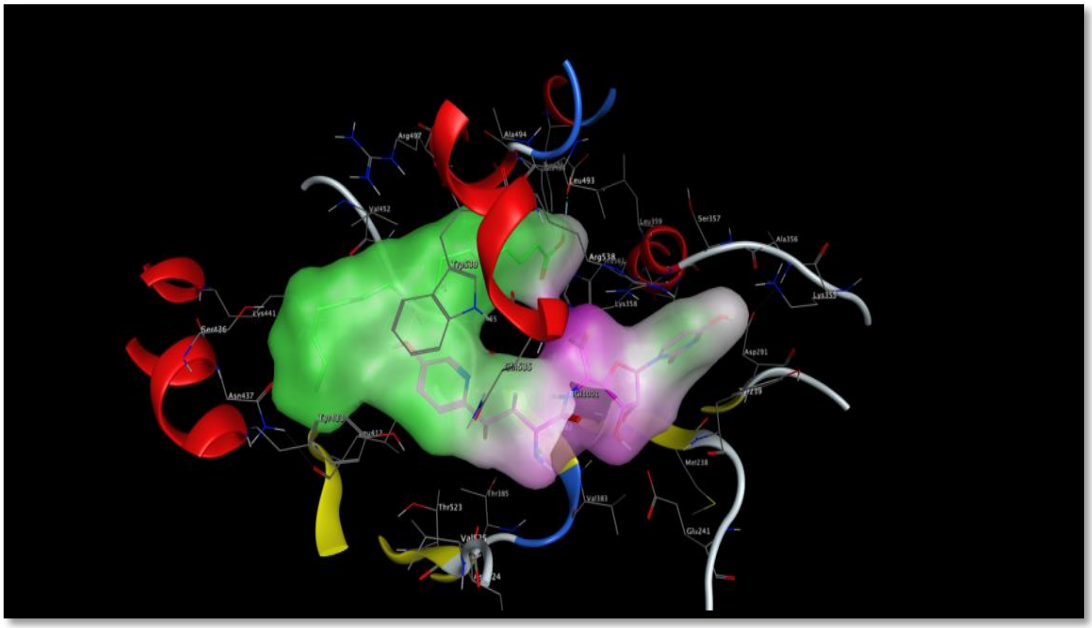


Figure 19: 7WJO - CID 985 pocket lipophilicity

Figure 20 shows that the binding site of 7WJO with the best Palmitic acid ligand is hydrophilic (lipophobic); the site is mainly colored purpel.

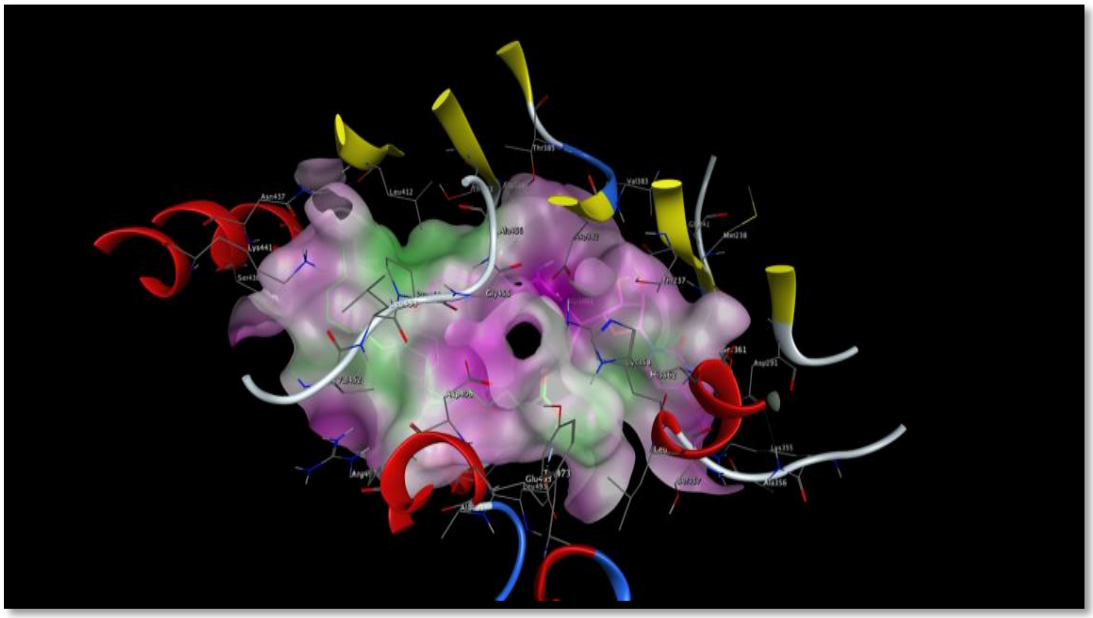


Figure 20: 7WJO - CID 985 lipophilicity

2. Discussion

Among the numerous *in silico* techniques described, molecular docking analysis is one of the most frequently used tools in drug design research and virtual screening studies to discover novel active molecules that are derived from natural sources **(Tonolo et al, 2023)**. It is a structure-based computational method that generates the binding pose and affinity between ligands and targets, and it has a crucial role in making drug discovery faster, cheaper, and more effective **(Muhammed & Aki-Yalcin, 2024).**

Molecular docking has become an essential part of a structural biologist's and medicinal chemist's toolkits. Given a chemical compound and the three-dimensional structure of a molecular target—for example, a protein—docking methods fit the compound into the target, predicting the compound's bound structure and binding energy. Docking can be used to discover novel ligands for a target by screening large virtual compound libraries. Docking can also provide a useful starting point for structure-based ligand optimization or for investigating a ligand's mechanism of action. Advances in computational methods, including both physics-based and machine learning approaches, as well as in complementary experimental techniques, are making docking an even more powerful tool **(Paggi & Dror, 2024).**

In our investigation, we examined *in silico* the effects of essential oils from *Pistacia atlatica* as potential fungicides. Nineteen of its compounds were chosen to be docked into the active site of two proteins (3G5T and 7WJO), using *MOE* software.

Pistacia atlantica Desf (wild pistachio), in English (*pistachio tree of the Atlas*) and in Arabic "*Betoum*" **(Mahjoub et al, 2018),** is one of the fruit, leaves and gum of *Baneh* have antibacterial, antifungal, cytotoxic, anticancer, anti-proliferative, antioxidant, antimutagenic and anti-inflammatory **(Naji-Tabasi et al, 2024).** It is the main herbal medicine that has been widely used in the Middle Eastern and Mediterranean areas since ancient time. In Algeria, *P. atlantica* is widespread from Mitidja (Northernparts) to the Saharan regions (South). It is usually found in the west up to the Zousfana region (near Bechar) and in the southeast Oranie area. It has been used in Algerian traditional medicines **(Achili et al, 2020).**

Since ancient times, *atlas pistachio* gum-like resin and fruits, very rich in essential oils (EOs) and fixed oils (FOs), respectively, were used in traditional medicine and included in different traditional cosmetics and health and beauty products **(El Zerey-Belaskri et al, 2022).** *P. atlantica* fruit oil is commonly called Bene Hull Oil (BHO)

constituting compounds such as carotene and tocopherols with antioxidant properties. It was shown to contain high amount (73.44%) of polyunsaturated fatty acids (PUFAs). Major PUFAs in that analysis included oleic acid (45.66%) and linolenic acid (24.21%) **(Mir Mohammad Sadegh et al, 2021).** Wild pistachio oil contains significant amounts of tocopherol (some form of vitamin E), sterols, antioxidant polyphenols, essential fatty acids, essential and non-essential amino acids, and minerals such as iron, sodium, copper, and zinc. Omega-3, -6 and -9, oleic acid, palmitic acid, linoleic acid, and arachidonic acid are of most important fatty acids found in wild pistachio **(Dogani et al, 2022).** The extraction of the essential oils was performed by the hydrodistillation technique **(Zerkani et al, 2022).** The seeds contained high concentrations of oil (32–67%). The major fatty acids were oleic (39–49%), linoleic (23.6–31%), and palmitic acids (21.3–26.6%) **(Labdelli et al, 2019).**

Furthermore, plants are a vast source of naturally occurring products, including the Secondary metabolites (SMs), that are the active ingredients in plants and are produced from the primary metabolic products, which are products necessary for human and animal body nutrition **(Benmohamed et al, 2023)**. They are complex and three-dimensionally oriented molecules that belong to diverse groups of organic compounds, which expand across the chemical space of known molecules **(De Felício et al, 2021).** These metabolites exhibit a wide range of biological activities, such as antimicrobial, antioxidant, and anticancer properties **(Selwal et al, 2023).** In addition, they contribute to the survival and health of plants and play a pivotal role in protecting them against abiotic (UV light, temperature, heavy metals, drought, salinity, etc.) as well as biotic stresses (herbivores, phytopathogens, fungi, bacteria, etc) **(Kajla et al, 2023).** Are exploited for their nutritive values, utilized as a source of medicinal components, and agrochemicals. Some of the plant secondary metabolites are beneficial to mankind as nutraceuticals and pharmaceuticals, that serve as an identifier for particular plant secondary products, e.g. monoterpenoids (essential oils), carotenoids (flower/fruits colours), or sesqui-, di- and triterpenes (phytoalexins, plant hormones) **(Mipeshwaree Devi et al, 2023).** In the plant kingdom, more than 2,140,000 secondary metabolites have been reported **(Al-Khayri et al, 2023).** They play a crucial role in helping plants cope with different stress conditions. **(Teoh & Teoh, 2016),** classified plant secondary metabolites into various groups based on functional groups and chemical structure. These groups include terpenes (including volatile compounds, sterols, and carotenoids), polysaccharides, phenolic compounds, phytoalexins (sulfur-containing compounds), alkaloids (nitrogen-containing compounds), flavonoids,

and hydrocarbons. Almost all of these metabolites contribute significantly to defense against stressful situations. Plant hormones, such as abscisic acid (ABA), jasmonates (JA), polyamines, and salicylic acid (SA), are also involved in responding to environmental stresses **(Reshi et al, 2023).**

Medicinal plants are an excellent source of different bioactive secondary metabolites **(Mohamed & Alotaibi, 2023).** With a recent move towards 'Greener Products' focused on sustainability, the scientific community has started showing interest in materials based on natural origin **(Sundar & Parikh, 2023).** Among these greener products, essential oils are very important natural products, which have different therapeutic and biological activities **(Moghaddam & Mehdizadeh, 2017).** against pests, insects, and pathogenic fungi…Their chemical composition is affected by several factors such as plant species or cultivar, geographical origin, environmental conditions, agricultural practices, and extraction method **(Assadpour et al, 2023).**

Essential oil, also defined as essence, volatile oil, etheric oil or aetheroleum **(Zerey-Belaskri et al, 2022)**, are natural, complex, and volatile mixtures of compounds with intense bioactivity that are extracted from various plant parts **(Oliveira et al, 2023).** They are produced as secondary metabolites by specialized secretory tissues in the leaves, seeds, flowers, bark and wood of the plant, and they play an important ecological role in plants **(Al-Khayri et al, 2023).** Their chemical composition is a complex mixture of naturally volatile compounds that account for the majority of their weight, such as terpenoids, aldehydes, esters, and alcohols, and nonvolatile compounds that account for a small portion of their weight, such as hydrocarbons, carotenoids, and fatty acids **(Ferreira & da Silva, 2023).** Some mosses, liverworts, seaweeds and some terrestrial and marine animals (sponges), insects, fungi, and microorganisms are also known to biosynthesise volatile compounds **(Zerey-Belaskri et al, 2022)**.

Essential oils or their volatile components cause critical defense strategies against herbivorous pests **(Ebadollahi et al, 2020).** They are eco-friendly and effective alternatives to the detrimental synthetic pesticides. And they demonstrate a range of biological activities, such as antiparasitic, antifungal, antibacterial, antiviral, antioxidant, anti-inflammatory... **(Sattayakhom et al, 2023).** They can use in different industries to control molds, various fungi and bacteria, such as food-borne and phytopatogenic organisms, which can cause various post-harvest diseases, animal and human disorders **(Mehdizadeh & Moghaddam, 2018).** More than 300 EOs are commercialized in the

fragrance and food markets, with anticipated growth reaching more than $15 billion by 2025 **(Yeshi & Wangchuk, 2022).**

In our study, the ligand *Palmitic acid* (CID-985) had the best results of the binding interaction with the protein 3G5T (Crystal structure of trans-aconitate 3-methyltransferase fromyeast), recording an S score of -8.0938; followed by *Linalyl propionate* (- 6.1474). Similarly, it gave the best S score (-6.7963) with the protein 7WJO (CryoEM structure of chitin synthase 1 from *Phytophthora sojae* complexed with nikkomycin Z).

In recent years, a number of studies have been carried out to test antifungal efficacy and physico-chemical characteristics *in silico.* For instance, **Fahloul & Laassami (2023)** has tested two target proteins 7WJO and 3G5T, and twenty of the chemical compounds from the essential oils of *Pistacia lentiscus*. He has found that the best S-scores (after the S-score of active molecules) were *T-Muurolol* with 7WJO, and *β-Myrcene* with 3G5T.

In another study, **Grine et al (2023)** focused on both the evaluation of the antifungal activity of *Pelargonium graveolens* essential oil against the citrus fungus *Fusarium proliferatum* and the *in-silico* study of its fractions. Their results showed a strong antifungal potential of all tested essential oil concentrations compared to the commercial fungicide Agriconazole. The *in silico DFT*, *ADMET*, molecular docking, and molecular dynamics studies confirm that the results have a greater affinity with the *in vitro* tests carried out for the selection of new antifungal products of natural origin, which suggests that the essential oil should be considered as an alternative natural source of chemicals.

Most of the plant species that grow in the world have therapeutic virtues; they contain bioactive molecules. Several of studies have also reported that the extracts contained in the various parts of *P. atlantica* have multiple biological activities, among which we cite the most important.

Hama Amin et al (2022) have studied antifungal activity of essential oil of *Pistica atlantica* kurdica, from the region of Halabja, a city in the north of Iraq. They assessed by testing different concentrations of oil gum (100, 50, 25 µl /ml) against *Aspergillus brasiliensis*. The results showed that the oil gum have strong antifungal activity because no growth was identified at different concentrations of the extract and the extract significantly inhibited growth of the *Aspergillus brasiliensis*. The data of this study suggested that *P. atlantica subsp. kurdica* oil gum has potential for application in pharmaceutical drugs against fungi.

In addition, another study of **Tarik et al (2021)** on EO from the leaves of *P. atlantica* growing in the Khenifra region (Morocco). This work revealed the correlation

between the antifungal activity against *Ascochyta rabiei*. After obtaining the oil by the hydrodistillation process, a chemical characterization was carried out by (GC –MS), the latter makes it possible to identify thirty-eight compounds, among them four in the majority which are: terpinen-4-ol (17.04%), α-pinene (16.03%), α-thujene (6.24%) and spathulenol (5.05%). Their test indicated that the essential oil of the leaves of *P. atlantica* had important antifungal activity against *Ascochyt rabiei* and the antifungal activity was achieved by the method of growth of fungi colonies on agar medium.

Furthermore, **Benabderrahmane et al (2009)** studied the antimicrobial activity of essential oils from *P. atlantica* Desf... resin, collected from three sites in western and south-western Algeria. They were tested *in vitro* on clinical isolates of seven bacterial strains (*Escherichia coli, Enterobacter cloacae, K. pneumoniae, Pseudomonas aeruginosa, Xanthomonas maltophila, Enterococcus feacalis and Staphylococcus aureus*) and three fungal strains (*Candida albicans, Candida albicansATCC20027 and Candida albicans ATCC20032*). Antibacterial potency was determined using the agar diffusion method. All extracts showed strong antimicrobial activity against fungal and bacterial strains at concentrations close to 105 µg/ml. Eos showed high antibacterial activity against *Staphylococcus aureus* and *Enterococcus feacalis,* with minimum inhibitory concentrations (MICs) below 10 µg/ml. *Candida albicans* showed strong resistance to the essential oils tested.

Besides, the antimicrobial activity of EOs from *P. atlantica* galls harvested in three regions (Aïn Oussara, Laghouat and Kheneg) was evaluated on seven pathogenic strains (*Escherichia coli*, *Bacillus cereus*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *MRSA+*, *Salmonella typhi* and *Candida albicans*), using agar diffusion, microdilution and microatmosphere methods (only for *Candida albicans*). EOs revealed a remarkable antimicrobial effect against the microorganisms tested, with MIC and MBC values ranging from 0.13 to 7.99 µl/ml and from 0.25 to 7.99 µl/ml, respectively. Significant activity was observed for samples from the Kheneg station against *Candida albicans* species, with a zone of inhibition of 68 mm (50 µl). These results suggest that the essential oils tested for their antimicrobial activity can be classified as bactericides **(Sifi et al, 2020).**

On the other hand, **Ahmed et al (2022)** studied the antioxidant activity of *P. atlantica* EO, by three antioxidant assays, 2,2 diphenyl-1-picrylhydrazyl (DPPH) and 2,2 azino-bis-(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) radical scavenging besides the ferric reducing antioxidant power (FRAP). They were applied to determine the total antioxidant activity in galls from both genders of *P. atlantica*. Fingerprints of ten *P.*

atlantica gall extracts were obtained by Ultra Performance Liquid Chromatography (UPLC). Extensive pre-treatment of the data and a linear multivariate calibration technique, Partial Least Squares (PLS), were used for model construction. The findings of the mentioned study highlighted that gender and harvest period affected the antioxidant activities and they suggest that *P. atlantica* gall might be used as an accessible source of natural antioxidants and for the treatment of diseases resulting from oxidative stress.

Another study **(Gourine et al, 2010)** on leaf EOs from leaves of *P. atlantica* Desf. collected randomly from four different locations in Algeria, reveals the promising potential of *P. atlantica* leaf essential oil as a source of natural antioxidants.

The association between proteins and ligands is governed by several thermodynamic parameters: hydrophobic interactions, electrostatic interactions, hydrogen bonds, solvation effects and entropy effects. Theoretically, the complex is favorable if the overall free energy variation of complexation is negative ($\Delta G_{complexation} < 0$) **(De oliveira, 2009).**

Electrostatic interactions, involved in ligand-protein binding events, can be roughly classified into three types; charge-charge, charge-dipole, and dipole-dipole. Typical charge-charge interactions are those between oppositely charged atoms, ligand functional groups, or protein side chains, such as positively charged (amine or imine groups, lysine, arginine, histidine) and negatively charged (carboxyl group, phosphate groups, glutamate side chain). An important contribution to the enthalpy change associated with a binding event arises from charge-dipole interactions, which are the interactions between ionised amino acid side chains and the dipole of the ligand moiety or water molecule. The dipole moments of the polar side chains of amino acid also affect their interaction with ligands **(Bronowska, 2011).**

The hydrogen bonds are classified based mainly on the strength of interaction as measured by the depth of the interaction potential at the minimum of the complex. Usually three classes are distinguished: weak, moderate, and strong bonds, with energetic boundaries at about 2 and 15 kcal/mol. The weak hydrogen bonds involve less polar X-H groups in proton donors, like C-H or P-H groups, or less polar acceptors, like the N2 molecule in the N2···HF. Also, the hydrogen bonds where X-H attaches to a π bond on the acceptor belong to this group. The weakest hydrogen bonds considered in the literature are about 0.5 kcal/mol. Most of hydrogen-bonded complexes of interest form the group of moderate hydrogen bonds. Water dimer or hydrogen fluoride dimer are typical examples for this group. Other well-known dimers in this group involve carboxylic acids, base pairs

of nucleic acids, and typical hydrogen bonds forming within or between proteins. The strong hydrogen bonds involve ionic species **(Szalewicz, 2001).**

The interactions between ligands and the hydrophobic side chains of proteins contribute significantly to the binding free energy. The hydrophobic residues mutually repel water and other polar groups and results in a net attraction of the non-polar groups of ligand. In addition, apolar and aromatic rings of tryptophan, phenylalanine, and tyrosine participate in "stacking" interactions with aromatic moieties of ligand. Many studies have demonstrated that the hydrophobic interactions, quantified by the amount of hydrophobic surface buried upon ligand binding, is the structural parameter correlating best with binding free energy **(Bissantz & Stahl, 2010 ; Perozzo & Scapozza, 2004).**

According to our study we found that, the binding site between the two target proteins (3G5T and 7WJO) and the best ligand "*Palmitic acid* "was characterized in general by hydrophobic interaction (lipophilic).

Conclusion And Recommendations

The use of synthetic chemicals in various sectors can cause mutagenic, carcinogenic and toxic effects on human health, and increase the rate of pollution in nature through the excessive application of synthetic fungicides. The aim of our study was therefore to find natural substances with activity to reduce the use of these synthetic products and solve problems associated with their application.

With a recent move towards 'Greener Products' focused on sustainability, the scientific community has started showing interest in materials based on natural origin. One such component is "essential oil", these natural extracts are well known for their as an alternative to synthetic fungicides for the control of fungal pests.

Thus, we studied *in silico* the antifungal activity of some molecules from *Pistacia atlantica* essential oils against two target proteins, by using molecular simulation software (MOE).

The results of *in silico* study showed that a good scores were obtained for the binding interaction of Palmitic acid (CID-985) with the two investigated enzymes: 3G5T (S score of -8.0938) and with 7WJO (S score of -6.7963). The binding site between the two target proteins (3G5T and 7WJO) and the best ligand "Palmitic acid" was characterized in general by hydrophobic interaction (lipophilic).

As perspectives, it is recommended to isolate this molecule, tested, and then used as an effective compound in the manufacture of biopesticides. Furthermore, to verify the results of this virtual study, the examined plant could be tested under laboratory conditions *in vitro* and then under real conditions in the field *in vivo*.

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Appendix

Chemical composition of essential oils of Pistacia atlantica (in %)

Pubchem code	Compound	Article 1	Article 2	Article 3
	α-Pinene	3,43	-	-
6616	Camphene	0,56	6,39	2,72
14896	β-Pinene	1,03	4,74	4,15
	o-Cymene	5,33	-	-
	Camphor	0,85	-	-
11230	Terpinen-4-ol	26,20	0,67	13,68
17100	α-Terpineol	4,32	2,76	4.48
6950273	Isobornyl acetate	1,65	-	-
	Thymol	1.00	-	-
	Carvacrol	0,84	-	-
	2-Ethyl menthone	0,85	-	-
	(E)-Caryophyllene	0,68	-	-
	γ-Muurolene	0,66	-	-
	α-Muurolene	0,73	-	-
92231	Spathulenol	7,73	12,92	7,87
	Caryophyllene oxide	4,37	-	-
	Globulol	1,88	3.80	1,29
92812	Ledol	1,03	1.95	0,52
	Cubeban-11-ol	0,91	-	-
	Junenol	1,12	-	-

6432005	γ-Eudesmol	1,54	1,66	1,54
3084331	epi-α-Muurolol	5,61	-	-
91753440	α-Muurolol	2,03	-	-
	Germacra-4(15),5,10(14)-trien-1-α-ol	0,97	-	-
	α-Cadinol	6,91	-	-
91746712	allo-Aromadendrene epoxide	1,79	1,68	tr
	2-Pentadecanone	1,55	-	-
	Hexadecanoic acid	3,45	-	-
	Phytol	2,33	tr	tr
	Tricyclene	-	1.94	0,85
	α -Pinene + α-Thujene	-	21.68	15.33
	Verbenene	-	tr	1,80
	δ -3-Carene	-	tr	tr
	α -Phellandrene	-	tr	0.72
7462	α -Terpinene	-	tr	3.93
	Limonene	-	0.71	0,73
	β-Phellandrene	-	tr	1,06
	trans-2-hexenal	-	tr	0,87
7461	Ɣ-Terpinene	-	tr	6.69
7463	p-Cymene	-	tr	2,70
	α -Terpinolene	-	tr	1.90

	6-Methyl-5-hepten-2-one	-	tr	tr
	(E)-3-Hexen-1,ol	-	tr	tr
	trans-2-Hexenol	-	tr	tr
	(Z)-3-Hexen-1,ol	-	0.46	0,53
	2-Hexen-1-ol	-	tr	tr
	β-Thujone	-	tr	0,91
	Bornylene	-	tr	0,72
	Linalool	-	tr	0,74
93009	Bornyl acetate	-	2.46	2,30
	Camphene hydrate	-	tr	tr
	Aromadendrene	-	1.68	tr
	allo-Aromadendrene	-	1.68	tr
	(E)-Pinocarveol	-	1.95	0,74
	Ledene	-	tr	tr
61098	Linalyl propionate	-	3.15	2,04
	α-Terpenyl acetate	-	0.41	3,79
13894537	Bicyclogermacrene	-	3.64	tr
	Germacrene B	-	0.56	0.62
	Geranyl acetone	-	tr	0.60
	Palustrol	-	0.48	tr
	Epiglobulol	-	0.40	0.70
	Viridiflorol	-	1.36	tr

14038848	Isospathulenol	-	2.60	2.77
	Myristic acid	-	tr	tr
985	Palmitic acid	-	1.41	0.96
	Myrcene	-	-	0,67

tr : traces

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